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Bachelor's thesis in Bachelor i Kjemi
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# Reducing Palladium leaching in the Suzuki-Miyaura cross-coupling reaction with two magnetic nanoparticle catalysts

## Katja L. Benestad

Supervisor: Odd-Reidar Gautun

A thesis presented for bachelors degree

in chemistry

## Abstract

This thesis is a literature study of Pd-leaching in the Suzuki-Miyaura reaction (SMC) with the two heterogeneous and magnetic **catalysts 1** an **2** developed by Wang et al. The authors measured Pd-leaching with trace-analysis, a hot-filtration test and a reusability test. **Catalyst 1** and **2** could react with 4-bromoacetophenone and phenylboronic acid with little leaching and yields between 96-99%, shown in Scheme 1. Recycled catalysts (after 21 runs) afforded similar results. **Catalyst 2** reacted better than **catalyst 1** with 4-chloroacetophenone in Scheme 2 with yields reaching 75% and little leaching. Both catalysts could be removed with an external magnet.
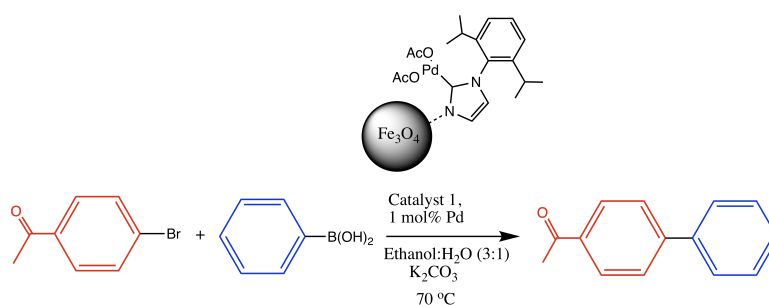


**Scheme 1:** Reaction between 4-bromoacetophenone (2 mmol), phenylboronic acid (2.4 mmol), $K_2O_3$ (3 mmol) and catalyst 1 (1 mol%) in ethanol-$H_2O$ (3:1, 20 mL).
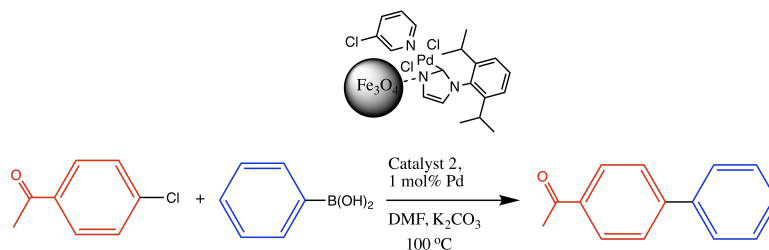


**Scheme 2:** Reaction between 4-chloroacetophenone (1 mmol), phenylboronic acid (1.2 mmol), $K_2O_3$ and catalyst 1 (1 mol%) in DMF (10 mL).

# Contents

# Definitions and abbreviations

CNT = Carbon nanotubes

HOMO = Highest Occupied Molecular Orbital

ICP-AES = Induced Coupled Plasma Atomic Emission Spectrometry

ICP-MS = Induced Coupled Plasma Mass Spectrometry

IUPAC = The International Union of Pure and Applied Chemistry

LOD = Limit of detection

LUMO = Lowest Unoccupied Molecular Orbital

M = Metal

MAGNP = Magnetic nanoparticle

MNP = Metal nanoparticle

MOF = Metal organic framework

NHC = N-Heterocyclic Carbene

NP = Nanoparticle

OECD = The Organization for Economic Cooperation and Development

PdNP = Palladium nanoparticle

SMC = Suzuki-Miyaura cross-coupling reaction

TON = Turn Over Number

UN = United Nations

XRD = X-ray diffraction

# 1 Introduction

The Suzuki-Miyaura cross-coupling reaction (SMC) was discovered in 1979, where a general synthesis of biaryls is shown in Scheme 3.[1] Since then, the reaction has become one of the most applied cross-coupling reactions in both academia and industry. For the last couple of decades, metal-catalyzed cross-coupling reactions have become widely popular, characterized by their efficiency and adaptability.[2] These reactions are involved in the synthesis of complex molecules, due to their reliability and versatility in creating new C-C and C-hetero atomic bonds..[3] SMC is popular for producing biaryls by using a palladium (Pd) catalyst.[4] Biaryls are particularly important for their broad application in medicinal chemistry, agrochemistry and other chemical industries.[5]
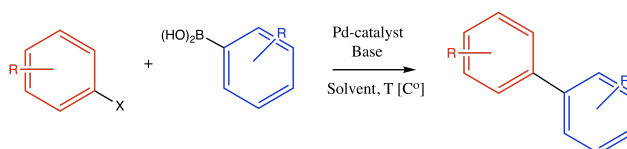


**Scheme 3:** General SMC producing biaryls. Drawing inspired by Bourouina et al.[6]

Metal contamination in the product and the solvent from metal leaching is one of multiple concerns when developing sustainable catalysts for cross-coupling reactions.[7] In addition, the high demand and high prices of Pd makes metal recyclability of interest in order to reduce costs.[3] This thesis aims to explore the question "How can Pd-leaching in SMC be reduced?" by looking at two catalysts developed by Wang et al. with Pd chelated to N-heterocyclic carbenes (Pd-NHC complexes) immobilized on magnetic carriers.[8] The catalysts are shown in Schemes 1 and 2. Magnetic Pd-catalysts have gathered interest due to their easy recovery, mild reaction conditions, potential ability for high yields and activity.[9] Although palladium nanoparticles (PdNPs) and Pd-leaching are not equivalent with each other, this thesis assumes that Wang et al.'s catalysts can prevent new PdNPs from forming in solution by preventing leaching. The catalyst structure, how yields and activity is affected by leaching, redeposition and reusability will be evaluated.

There is a lot of literature on recovering Pd, as it's an expensive metal and toxic for the environment.[10] Sustainable chemistry, also sometimes referred to as green chemistry, is increasing in importance when developing chemical processes. Development of recyclable heterogeneous transition metal catalysts have been a focus in sustainable synthesis in order to minimize health-and environmental concerns and production costs.[7] Heterogeneous catalysis is defined as "*the process in which reaction occurs at or near an interphase between phases*".[3] In order to discuss the sustainability of the catalyst, this thesis will look at its ability to perform in green media like water or water-alcohol mixes. Research on an appropriate solvent for a

reaction is a different angle on the green chemistry issue and could be presented as its own thesis. Although SMC is able to perform with other more sustainable metals, there is still an interest to look at how Pd-mediated reactions can be more sustainable as Pd is one of the most applied catalysts.

## 2  Theory

### 2.1  Conventions for green chemistry

There is a need for a common understanding of the terms "sustainable" and "green" in chemistry in order to discuss how SMC can become more sustainable. The International Union of Pure and Applied Chemistry (IUPAC) defines sustainable chemistry, as defined by the Organization for Economic Cooperation and Development (OECD) in 1999, as the "*[...] design, manufacture and use of environmentally benign chemical products and processes that prevent pollution, reduce or eliminate the use and generation of hazardous waste, and reduce risk to human health and to the environment*".[11] Additionally IUPAC adopted the related term "green chemistry" in the 2000s, as "The invention, design, and application of chemical products and processes to reduce or to eliminate the use and generation of hazardous substances".[12] The United Nations (UN) has made 10 specific objectives and guiding considerations for green and sustainable chemistry, shown in Figure 2.1.[13] Four of them are relevant for catalyst development in SMC and are as follows: Advancing sustainability of production processes, minimizing chemical releases, avoiding regrettable substitutions and pollution and developing solutions for sustainability challenges.[13]

Separation and reusability of noble metal catalysts are trends in catalysis that follows the development of green chemistry.[8] Although PdNP pollution is mainly from motor vehicles, there are increasing regulations in chemical industry about avoiding PdNP and palladium pollution from chemical waste.[10] SMC is an important reaction in the pharmaceutical industry and has to be regulated related in relation to health and environmental concerns.[7] The degree of environmental impact from a chemical process is largely evaluated from the solvent and waste.[14] Green chemistry requirements are supposed to navigate industry towards sustainable processes which will also bring about other advantages, such as reduced production costs, faster processes, increased capacity and energy savings.

**Figure 2.1:** The 10 objectives and guidelines for sustainable chemistry. Drawing is inspired by the UNs website[13]

## 2.2 The fundementals of SMC

### 2.2.1 The catalytic cycle

SMC is known as the most efficient and is among the most common Pd-catalyzed reactions in pharmaceutical synthesis.[3] It is the coupling of an aryl, a vinyl or a sulfonate with boronic acids, boronate esters or boranes in basic conditions with a Pd(0) catalyst present.[15] This is shown in in Scheme 3. SMC has an advantage over many reactions.[16] The reaction has a large variety of applications, reagents and products.[4] It is able to react with many commercially available reagents that are inert with water and thermodynamically stable. SMC can react with functional groups with low toxicity and produce non-toxic by-products. Cross-coupling reactions often involve an organic electrophile ($R_1$-X) being attacked by an organometallic nucleophile ($R_2$-M) in the presence of a metal catalyst and a base.[17] Depending on the catalyst, metal mediated cross-coupling reactions can be performed at mild reaction conditions.[3]

SMC reacts in a catalytic cycle, consisting of the 3 steps: oxidative addition of aryl halide to Pd-catalyst, transmetalation by adding organoboron compound and reductive elimination
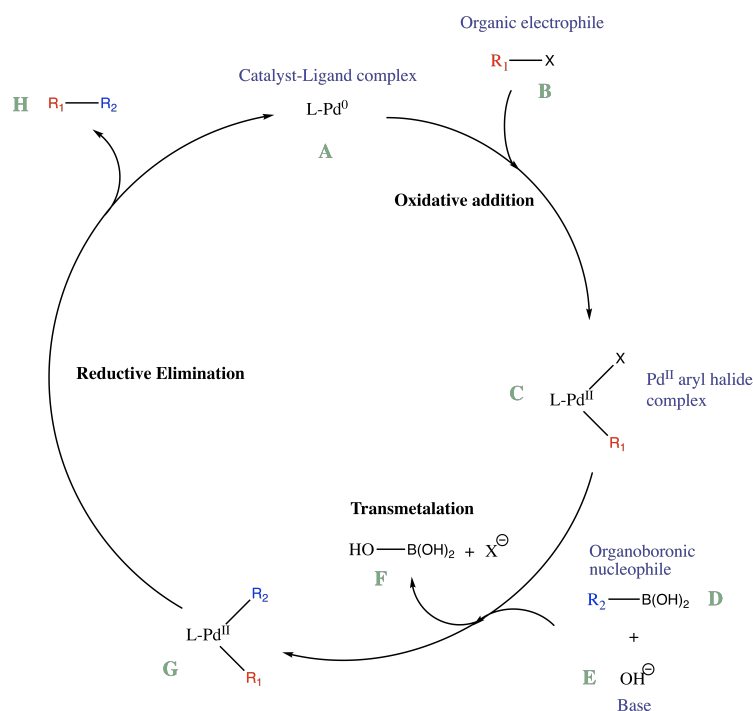
**Scheme 4:** General catalytic cycle and mechanism for SMC, showing oxidative addition, transmetalation and reductive elimination. Inspired by Mukai and Yamada.[7]

of the catalyst.[7] The catalytic cycle is shown in Scheme 4. Oxidative addition is assumed to be the rate determining step.[1] The catalyst has the ability to weaken the electrophile's $R_1$-X bond (compound B in Scheme 4), where X represents a halide and $R_1$ is an aryl moiety.[5] The catalytic cycle starts with oxidative addition, changing the valency of palladium from 0 to +2. This results in compound C in Scheme 4. Generally, the relative reactivity followed the order $R_1$-I> $R_1$-OTf, $R_1$-Br » $R_1$-Cl.[4] Base catalysis is often required when a boronic acid is used (D in Scheme 4).[18] The base helps form a more reactive boronate ion in the transmetalation step. The base substitutes the halide in favour of a hydroxylgroup (OH) before the catalytic cycle continues to G. Transferral of the organic group from the organoboron compounds onto G occurs via transmetalation.[5] In this step, palladium and boron exhange OH with the aryl moiety $R_2$. Following the transmetalation is the reductive elimination step, which promotes the formation of the $R_1$-$R_2$ products and is seen as H in Scheme 4. The last step involves regeneration of Palladium(0).

## 2.3 Catalysts in SMC

Heterogeneous catalysts are commonly used in chemical industry, such as in ammonia-production with the Haber-Bosch process, while homogeneous catalysts are most common in fine chemical industry like pharmaceuticals.[3] Homogeneous catalysts are often used in cross-coupling reactions due to their commercial availability and high catalytic activity. They have many ad-

vantages, such as displaying high activities with better understood mechanisms.[4] The biggest issues when using soluble complexes in cross coupling reactions is leaching, difficult catalyst separation, product contamination and the low possibility of reusing the catalyst.[19] Applications of homogeneous catalysts are therefore becoming more restricted in chemical and pharmaceutical industries. SMC can use a heterogeneous metal complex as catalyst, where a central metal core is surrounded by organic electron-donating ligands.[20] Transition metals in groups 8-10 in the periodic system, like palladium and Nickel, are commonly used in cross-coupling due to their ease in performing in redox reactions and changing oxidation states.[17]

### 2.3.1 Properties of catalysts

Some parameters may be defined in order to evaluate efficiency and catalytic activity. The turn over number (TON) is a unitless quantity used to measure catalyst activity by evaluating the number of turns per catalytic cycle, or moles of molecules reacted per mol of added catalysts.[21] This is shown in equation 2.1 The higher the values, the more active and efficient the catalyst.[20]

$$TON = \frac{n_{product}}{n_{cat}} \tag{2.1}$$

### 2.3.2 Nanoparticles as catalysts in SMC

Nanoparticles (NPs) are rising in significance in the field of catalysis.[22] PdNPs became popular catalysts for SMC after it was discovered that escaped atomic palladium from a homogeneous Pd-complex would aggregate into PdNPs.[23] Complexes with palladium weakly bound to ligands tend to collapse, releasing atomic palladium into solution during oxidative addition. It is assumed that NPs and Pd-complexes can act as a source of metal species leaching into solution, acting more like precatalysts. The term precatalyst is used for a compound that must undergo chemical change in the initial stages of reaction in order to deliver the true catalytic species.[24]

Pd-leaching from catalyst is typical for cross-coupling reactions, where metal leaches into the solution and product.[14] Leaching is the phenomenon where metal ions are released into the solvent from the central core of the catalyst, resulting in the deactivation of the catalyst.[7] Palladium leached from PdNPs or Pd-complexes can result in Pd-clusters and molecular $Pd^{2+}$ contaminating the solution and the product.[5] Solvents are responsible for most of the waste in pharmaceutical industry.[25] Thus it is of interest to reduce homogeneous catalysts, like leached palladium atoms and naked PdNPs, in solution.[14] Introducing catalysts that do not leach palladium or catalysts that can recapture leached palladium allows for a process that may be reused multiple times and prevents pollution into solvent and product contamination.[23]
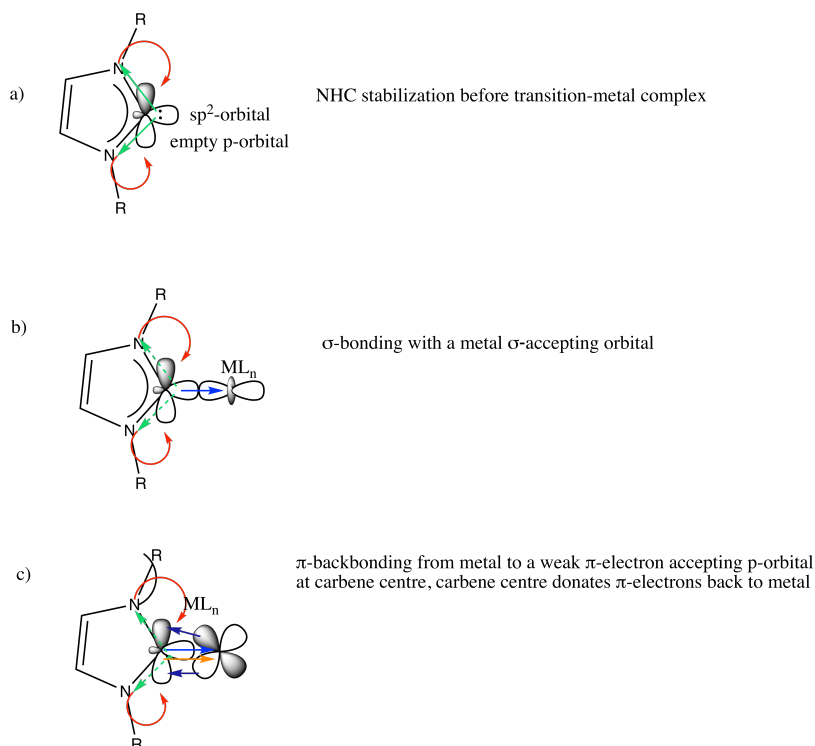
### 2.3.3 NHC ligands

Ligands and supports are important in preventing catalyst destabilization during reaction, like agglomeration and Pd-leaching.[19] Catalysts can be chelated with NHC that are more stable than most electron rich ligands and are easily modified into structurally diverse analogues.[8] Figure 2.2 shows a general NHC as a ligand in organometallic catalysts. NHCs are heterocyclic compounds containing a carbene, shown in Figure 2.2, with at least one nitrogen in a ringstructure.[26] NHC is often used for homogeneous catalysts. The highest occupied molecular orbital (HOMO) for the carbene carbon in NHC is a lone-pair in a $sp^2$-orbital and the lowest unoccupied molecular orbital (LUMO) is an empty p-orbital. NHC is electronically stabilized inductively by $\sigma$-electron withdrawing interactions and mesomerically by $\pi$-donating interactions with neighbouring nitrogens. This is illustrated as drawing a in Figure 2.3. The inductive effect decreases the energy of HOMO, whilst $\pi$-donation into carbons LUMO distributes electrons between more atoms. By having more electron donating groups substituted onto nitrogen, like the bulky arylmoiety seen in Wang et al.'s catalysts in Figure 2.4, increases the mesomeric effect. Bulky substituted groups on nitrogen adjacent to carbene also influences the $\sigma$-donation in other metal-ligand bonds. It could stabilize the catalyst by preventing unwanted compounds from reacting at metal centre or destabilize it by making it more difficult for other ligands to bind to the metal.

NHC                                              Carbene



M = Pd, Ni, Rh
L = ligands
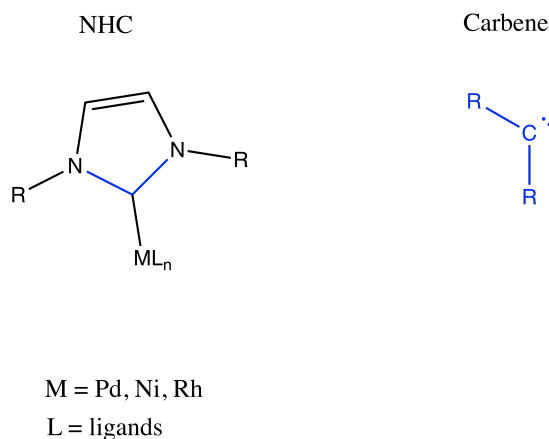
**Figure 2.2:** General NHC and carbene. Inspired by Hopkinson et al.[26]

The lone pair makes the compound nucleophilic and makes NHC able to have strong $\sigma$-interactions with metal.[26] Stabilized carbenes bond to a metal by strongly donating the lone-pair of electrons into $\sigma$-accepting orbital in a transition-metal complex, resulting in an electron rich metal centre. This is seen as drawing b in Figure 2.3. Drawing c illustrates the additional $\pi$-backbonding from electron dense d-orbitals in the metal to the carbene's LUMO. $\pi$-backbonding increase as mesomeric interactions increases. LUMO is a weak $\pi$-electron ac-

ceptor, due to the mesomeric effect already being present, resulting in $\pi$-donation from carbene back to the metal. This results in a very strong bond between NHC ligand and metal. The metal chelated with NHC is more activated for oxidative addition, seen in Scheme 5.[26] Stronger electron-donating ligands will make it easier to react with difficult reagents, like aryl chlorides. Large steric influences from NHC can result in more favourable reductive elimination.



**Figure 2.3:** a) Illustrates NHC ligand before it is in a transition metal complex. The green arrows represent inductive $\sigma$-withdrawal and the red represents mesomeric $\pi$-donation. b) Illustrates the $\sigma$-bond to a d-orbital in the metal. Blue arrow represents $\sigma$-donation. c) Shows $\pi$-backbonding with dark blue arrows and $\pi$-donation from carbene with orange arrow.
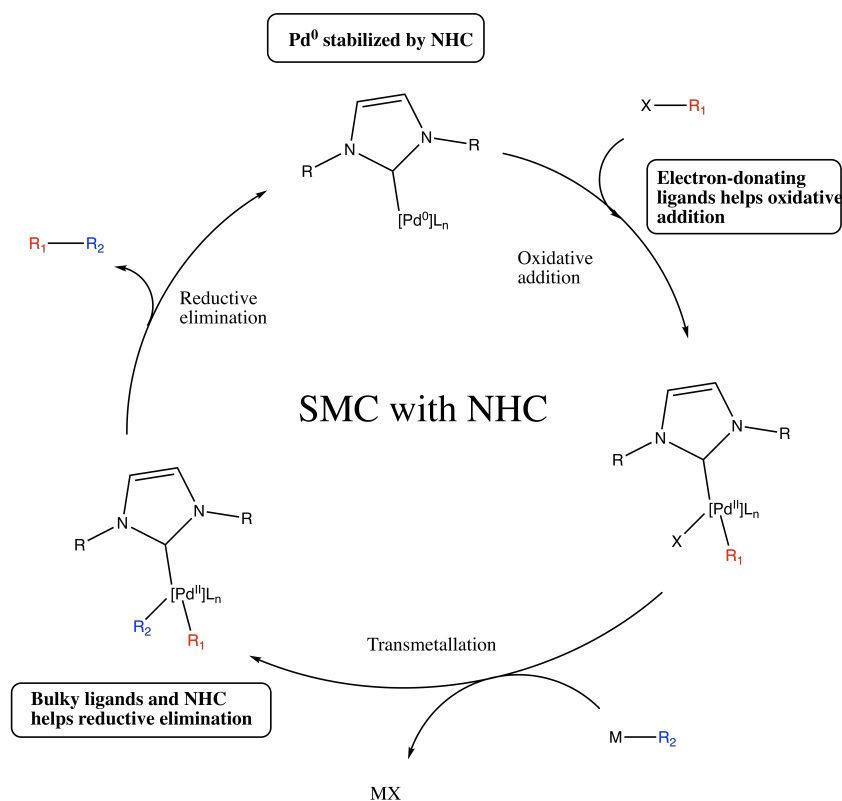
**Scheme 5:** SMC cycle with NHC as a ligand. Inspired by[26]

## 2.4 Palladium chelated to magnetic nanoparticles

There has been a growing interest in heterogeneous catalysts due to the possibility of easier recovery and recycling of metal.[9] Superparamagnetic NPs have been developed as supports for Pd-catalysts to modify soluble catalysts into heterogeneous catalysts.[8] The benefits of NP carriers are deposit-free, nanosize distribution, easy separation and non-toxicity. Iron oxides ($Fe_xO_y$) are most common and allow for a wide range of different attachment strategies.[9] Wang et al. developed $Fe_3O_4$ NPs immobilized with NHC-Pd catalysts ($Fe_3O_4$-NHC-Pd) that could react with a range of different aryl bromides and boronic acids.[8] These are presented as **Catalyst 1** and **2** in Figure 2.4.

MAGNPs and magnetic materials show paramagnetic character, thus the catalyst may be removed by simply using an external magnet.[22] Materials such as silica ($SiO_2$) can be applied to the $Fe_xO_y$ surface to immobilize different organic ligands or functional groups. These can anchor or recapture palladium by forming metal-organic complexes. Functional groups play an important role in the mechanism of Pd-leaching.[5] The versatility of $Fe_xO_y$ allows for many different ligands that may chelate to Pd, keeping the catalyst attached to MAGNPs.[9]
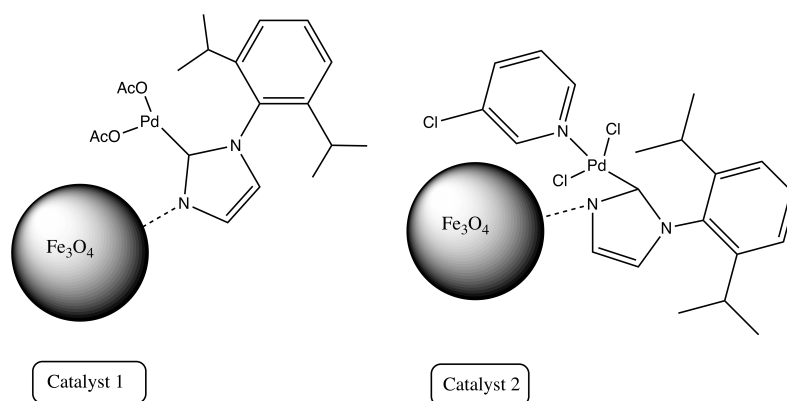
**Figure 2.4: Catalyst 1** and **2** developed by Wang et al. Figure inspired by Wang et al.[8]

## 2.5 Measuring Pd-leaching

The hot-filtration test and reusability test are two of the most common methods of measuring Pd-leaching.[6] The hot-filtration test is often used to indicate whether leached species contribute to the conversion of the product. It is performed by removing the catalyst from the solution at constant reaction temperature to check whether the reaction continues in the solution. The reusability test consists of reusing the catalyst in a new batch or several successive runs with new reactants.

Pd-trace concentration analysis of the solution is often used to evaluate the degree of Pd-leaching and can be used alongside hot-filtration and reusability tests.[6] Trace metal detection can be conducted by Inductive coupled plasma atomic emission spectroscopy (ICP-AES) or Inductive coupled plasma mass spectroscopy (ICP-MS). Both use ICP, mainly plasma, as ion source to excite atoms or create ions.[27] The AES and MS detectors are different. AES are detectors that rapidly, accurately and precisely measure composition from radiation of energy transitions in excited atoms.[28] ICP-MS measures the intensities of elements and mass/charge of ions in the sample. It is capable of measuring elements at low concentrations due to a lower limit of detection (LOD). X-ray diffraction (XRD) measures the molecular structure and concentration of materials by analysing the absorption of scattered light.[29] Resulting spectra is a diffraction pattern, allowing qualitative comparisons of spectra before and after reactions.

## 3 Discussion

Pd-leaching is a notable challenge for heterogeneous catalysts.[7] Application of palladium continues to increase in many chemical and bioindustrial sectors, thus contributing to the global distribution of PdNPs.[10] This increases the chance of exposure in living organisms.[10] Pd, particularly PdNPs, released into the environment is a source of environmental pollution. Leaching
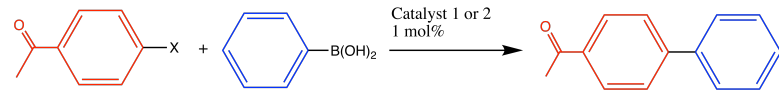
may cause metal contamination in the product and may make the catalyst less reusable. Due to this, extra purification steps could be required to remove the contaminants, which would increase production costs. Leached palladium is assumed to be able to form new catalytically active species, like new PdNP or Pd-complexes, in solution. This suggests that heterogeneously designed catalysts may operate similarly to a homogeneous catalyst to some degree.[5] Reducing leaching can thus minimize chemical hazards, chemical releases, cost, pollution and protect consumers, as adviced in UNs model shown in Figure 2.1.
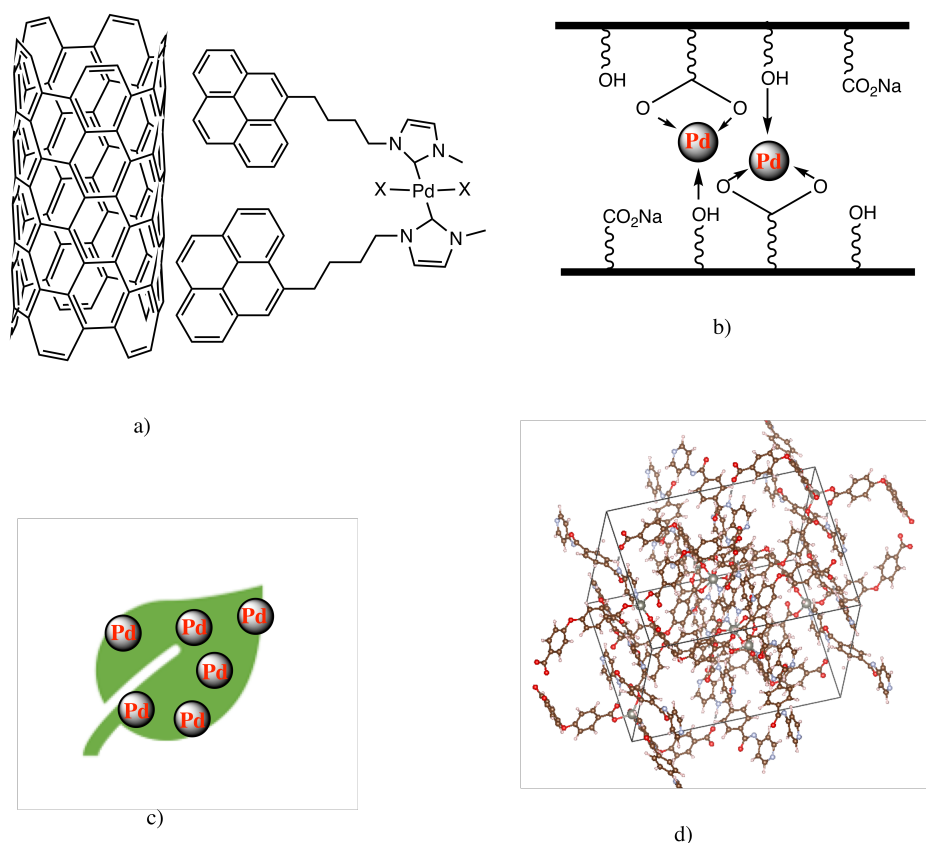


**Figure 3.1:** a) Single-walled CNT catalyst bound to NHC-complex, b) PdNPs on carboxymethylcellulose catalyst, c) PdNPs immobilized by biopolymers on black tea leaves. Drawings inspired by Chergui et al. Xiao et al and Lebaschi et al[30–32] d) Shows $ZnH_{15}C_{23}(NO3)_2$ as an example of a MOF.

Knowledge of a general mechanism for leaching in heterogeneous catalysis is limited, where the mechanism can currently only be described empirically.[22] There have been developed many different heterogeneous catalysts that can be recycled, like palladium immobilized on charcoal (Pd/C), immobilized on carbon nanotubes (CNTs), biopolymer supported PdNPs such as tealeaves and cellulose, and PdNPs supported on metal organic frameworks (MOFs).[2,9] Some of these catalysts are shown in Figure 3.1. Although they are sufficient catalysts that are suitable for recycling, few of them are easily separated from the reaction mixture despite being assumed as heterogeneous. Wang et al.'s catalysts in Figure 2.4 are easily recovered, recycled and experience little leaching.[8]

**Table 3.1:** Comparison of arylhalide, yields and Pd-leaching into product for **Catalyst 1** and **2**. [a] **Catalyst 1** (1 mol%, 0.02 mol% Pd), 4-bromoacetophenone (1 mmol), phenylboronic acid (1.2 mmol) and $K_2CO_3$ were added to 2:1 ethanol water (10 mL)for 12h. [b] **Catalyst 2** (1 mol%, 0.02 mol% Pd), 4-chloroacetophenone (1 mmol), phenylboronic acid (2 mmol) and $K_2CO_3$ were added to DMF (10 mL)for 12h. Data from Wang et al.[8]



| Catalyst | X = Halide | Temperature [°C] | Yield [%] | Pd leached into product |
|---|---|---|---|---|
| $1^a$ | Br | 70 | 96-99 | <0.1 ppm |
| $1^a$ | Cl | 70 | Trace | 2.5% |
| $1^a$ | Cl | 100 | 72 | 4% |
| $2^b$ | Cl | 100 | 74 | <1 ppm |

There are two major strategies to minimize Pd-leaching.[7] The first approach is to modify reaction conditions, changing solvents and reaction temperatures. However, this is not a practical solution for industrial settings, as the reaction conditions would need adjustment for every run. The second method is to introduce supporting materials that may stabilize the catalyst. MAGNPs can be modified with stabilizing functional groups, like NHC, to reduce leaching and increase reusability.[7] Wang et al. used stable NHC ligands that, due to strong $\sigma$-interactions and $\pi$-backdonation were able to form strong NHC-Pd bonds.[26] This was shown in Figure 2.3. NHCs are beneficial in heterogeneous catalysts due to being able to stabilize transition-metal NPs. The heterogeneous **Catalyst 1** and **2** from Figure 2.4 mimic some of the most stable homogeneous NHC-complex catalysts in SMC, like phosphines.[26] The strong NHC-Pd bond lowers the rate of catalyst decomposition by making metal richer with electrons. When **Catalyst 1** reacted with 4-bromoacetophenone and phenylboronic acid, as seen in entry 1 in Table 3.1, there was observed less than 0.1 ppm leached palladium in the product when measured with ICP-AES.[8] ICP-AES showed that palladium content in the catalyst only changed a little. More than 99.8 % of palladium was still retained on magnetic support.[8] The LOD of the ICP-AES was 5 ppb Pd, which was sufficient to measure Pd-leaching for **catalyst 1**. Optimized ligands that anchor the active catalyst to the magnetic carrier have produced sufficient catalytic systems that minimizes catalyst leaching, even after many cycles.[33]

Pd-leaching was minimized for the reaction in Scheme 6, as NHC was able to improve stability through its electronic and steric interactions.[8] Particularly for **Catalyst 1** and **2**, the arylmoiety on one of the nitrogens might have been electron donating enough that it helped increase the $\pi$-backbonding. This also increased the NHC-Pd bond strength. This may have activated the metal centre more towards oxidative addition, where the bulkiness of the arylmoiety may have prevented unwanted reagents from reacting and made reductive elimination more favourable. The reaction is shown in Scheme 6. The structure of **Catalyst 1**, as seen in Figure 2.4, was measured by XRD before and after use. Wang et al. found no characteristic peak for

PdNPs when 0.023 mmol$g^{-1}$ **catalyst 1** was used.[8] As no PdNP peaks were observed with XRD, it was assumed that no palladium was leached into the solution and catalytic activity could mainly be attributed to **catalyst 1**.
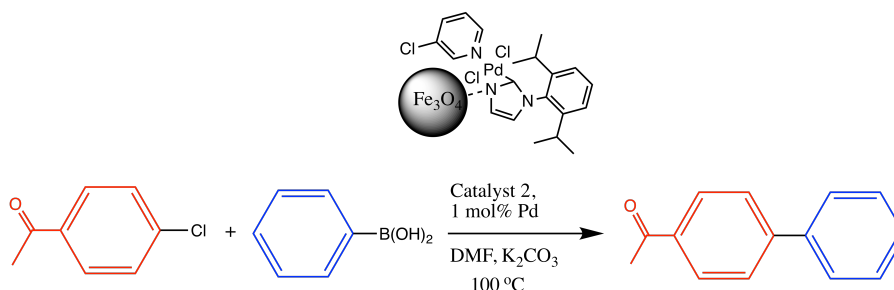


**Scheme 6:** Reaction between 4-bromoacetophenone, phenylboronic acid and **catalyst 1**

A disadvantage with MAGNPs with Pd-complexes is the difficulty of reacting with aryl chlorides.[8] Wang et al.'s catalysts performed worse when having to break the C-Cl bond at 70 °C, where the yield of **catalyst 1** in entry 2 in Table 3.1 decreased greatly. Aryl chlorides are more attractive in industry than aryl bromides due to their inexpensiveness and availability. However, harsher reacting conditions are typically required when activating C-Cl bonds. In comparison to reacting with aryl chlorides, **catalyst 1** could get higher yields with aryl bromides at 70 °C which is seen from entry 1 in Table 3.1. The conversion improved when increasing temperature to 100 °C in entry 3, however, Pd-leaching of **catalyst 1** in the product increased significantly from 2.5% to 4%. Leaching can be temperature dependent, where high temperatures and otherwise harsh conditions could contribute to increased leaching.
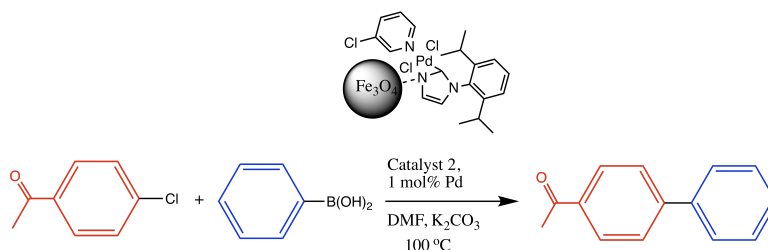


**Scheme 7: Catalyst 2** reacting at 100 °C with 4-chloroacetophenone and phenylboronic acid

It was believed by Wang et al. that aryl chlorides could coordinate to palladium in such a way during oxidative addition that it could result in the disintegration of the chelate structure for **catalyst 1**.[8] Only one of the nitrogens were bound to a bulky functional group. The other nitrogen was bound to $Fe_3O_4$, making **catalyst 1** less sterically hindered compared to if it had two bulky substituted groups. This may have reduced mesomeric affects, making metal centre of **catalyst 1** less electron dense during oxidative addition, giving aryl chloride an opportunity to break the chelate structure.[26] Yet, **catalyst 2** in Figure 2.4 performed well even at 100 °C

during the reaction in Scheme 7. Seen for entry 4 in Table 3.1, **catalyst 2** reached a yield of 74% and Pd-leaching was at less than 1 ppm. This indicated that the structure of **catalyst 2** was stable enough to prevent aryl chloride from interfering with the chelate.[8] **Catalyst 2** used a 3-chloropyridine as a ligand, which made the Pd-complex in **catalyst 2** more stable than **catalyst 1**. This could have been due to the extra $\sigma$-electron donating effects from pyridine making Pd more electron rich and increasing the catalyst stability. Or it could be from the additional steric hindrance that is provided by an additional ring. The pyridine may have made the NHC-Pd complex in **catalyst 2** less liable than for **catalyst 2**, showing how changing the ligands changes the stability. As seen from Wang et al., the catalyst structure is an important factor when reducing leaching.

**Table 3.2:** Table showing yields of product for **catalyst 1** in reaction seen in Scheme 6 after 21 consecutive runs. Data from Wang et al.[8]



| Run | 1 | 3 | 5 | 8 | 12 | 15 | 18 | 21 |
|---|---|---|---|---|---|---|---|---|
| Yield [%] | 96 | 97 | 99 | 99 | 93 | 98 | 96 | 97 |
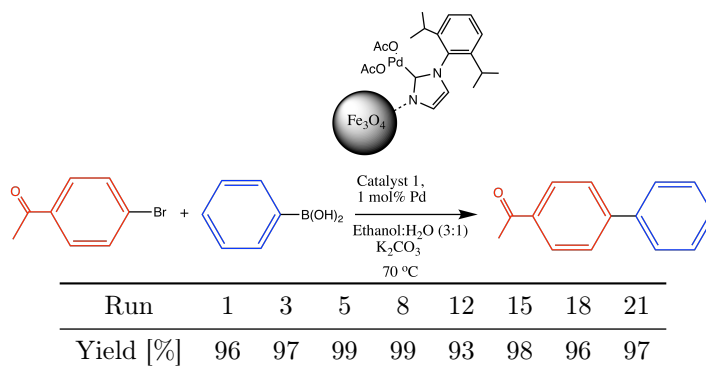
When yield decreases rapidly during recycling, it can be thought that the catalyst experiences Pd-leaching.[4] Fareghi-Alamdari et al.s' catalyst with Pd-NHC immobilized on sillica coated MAGNPs, seen in Figure 3.2, experienced this.[6] The catalyst could perform 6 successive runs at 80°C, however the yield decreased during the last experiment by 97-88%. 0.15% leached palladium was found with ICP-AES. Dong et al. supported PdNP on a MOF-5-derived nanoporous carbon which exeperienced a decrease from 90–98% after 5 runs.[34] The decrease was assumed to result from Pd-leaching, which was measured to be 4.4-4.8%. **Catalyst 1** seemed to not experience this, as the yield in Table 3.2 stays around 93-99% after 21 runs in Table 3.2.[8] Wang et al. reported that **catalyst 1** experienced a 6% decrease between runs 8 and 12, yet it is unknown for the readers if the decrease is gradual or sudden between runs 11 and 12. However, having a 6% during the total of 21 runs indicates that yield did not decrease rapidly and Pd-leaching was not assumed.
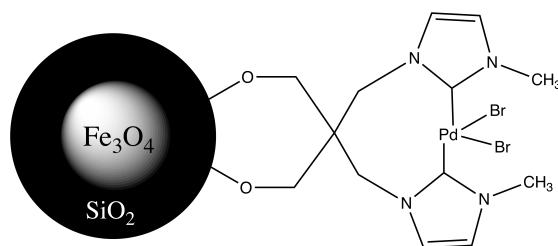
**Figure 3.2:** Pd-NHC immobilized on sillica coated MAGNPs. Figure inspired by Fareghi-Alamdari et al.[35]

Wang et al. performed recycling experiments, which showed that yields were nearly unchanged after 21 repeated runs for reaction in scheme 6 seen in Table 3.2.[8] The reusability test does not prove that the mechanism is heterogeneous without leaching.[6] However, the tests can be informative about whether palladium re-capture is effective if yields are similar. In Table 3.2 the yields are constantly above 90%, indicating re-capture if palladium was leached. Yields varied between 93, 99 and 96% for the first run and was at 97% for the $21^{st}$ run. The reusability of the MAGNP catalysts in Wang et al.'s report indicates the potential of magnetic catalysts in large scale applications, with practically no Pd-leaching.[8] The MAGNP catalysts demonstrates high degree of recyclability. The extreme stability in their catalysts might be due to stable ligands like NHC.

Bourouina et al. states that Pd-leaching always occur for putative heterogeneous catalysts.[6] Palladium may leach into the solution, act as a catalyst and redeposit itself back onto the heterogeneous support. Thus, Pd-leaching may occur whenever during a SMC, even when small concentrations of leached palladium after the final run is measured. For every experiment where soluble Pd-species are identified, it will be difficult to draw conclusions about a true heterogeneous catalyst. Thus, it will imply that most heterogeneous Pd-catalysts, like Pd-complexes immobilized on MAGNPs, can experience Pd-leaching to some degree. Small amounts of leached species may act as the actual catalysts during SMC.

Assuming that Bourouina et al. used leached palladium to represent new PdNPs or Pd-complexes formed in the solution, this could contribute to PdNPs contaminating the solvent and product. $Fe_xO_y$ species showcase an ability allowing the recapture of leached palladium onto their surfaces.[9] Thus, leaching could have occurred at some point during Wang et al.'s experiments. Bourouina et al. seemed eager to prove that Pd-leaching occurs for all catalysts.[6] Particularly that the leached palladium concentrations, even 0.15% for the catalyst in Figure 3.2, was significant and could effect SMC. On the other hand, trace-amounts of PdNP in solution may not have as dire effects as Bourouina et al. would have it. Although, in an ideal world, one would want to be able to fully separate palladium from the mixture with the catalyst.

One cannot assume that Pd-leaching does not occur without doubt during a reaction, even if solvent contamination is avoided. An interesting question to ask is why it would be a problem if palladium has leached, acted as a catalyst, and then redeposits itself back to its original catalytic form. Leached palladium may coalesce to form other catalytic active species in solution.[6] A part of wanting to reduce Pd-leaching is to avoid byproducts and contaminating the product with trace metal.[8] If putative heterogeneous catalysts leach homogeneous catalysts in the reaction, yet redeposits palladium back to the heterogeneous catalyst, it could result in a larger degree of impurity in the product. Thus, constant analysis of product purity would be required which would cost resources and time. In terms of avoiding palladium being thrown away with the waste, redepositing will be beneficial. On the other hand, because of the high requirements for purity of products in the pharmaceutical industry, avoiding byproducts and impurities is important.[8]

Wang et al. performed hot-filtration tests with **catalyst 1** for the reaction seen in Scheme 6.[8] **Catalyst 1** was removed after the coupling reaction in Scheme 6 had gone for 1 h with 73% conversion. The conversion in the last run for the reaction in Scheme 6 was 73.8% after 12 h. This further indicated that no palladium had leached into the solution during the reaction, supporting that catalytic activity mainly depended on **catalyst 1**. Comparing runs 1 and 2 in a hot-filtration test when conversion is 30-70% can be informative by comparing conversion. If conversion is not the same for both runs reacting with the same conditions, this will indicate that the catalyst was modified due to Pd-leaching or deactivation.[6] Wang et al. only reported yields for the first and third run seen in Table 3.2.[8] These have approximately the same yields, thus it may be assumed that catalyst was not significantly modified.

High catalytic activity may be desired in some cases, whilst avoided in others. Catalysts with higher activities are usually less stable and exhibit poorer selectivity, which can result in lower yields with more byproducts and inactivation of catalyst in storage.[8] Yamamoto et al. immobilized PdNPs on graphene oxide which showed high catalytic activity with TON exceeding 100 000 and yields between 44-99% in comparison to **Catalyst 1**.[36] **Catalyst 1** in Figure 2.4 was able to maintain high activity with TONs around 4800-4950 as seen in entry 1 in Table 3.1 for the reaction shown in Scheme 6.[8] **Catalyst 1** acted as a quasi-homogeneous phase in the solvent by being uniformly dispersed throughout the liquid due to superparamagnetism. This effect, alongside spatial restrictions and electrostatic interactions from ligands, kept **catalyst 1** particles from aggregating or agglomerating. The activity of the Pd-NHC complex may have benefitted from the dispersion, as surface area was increased. Even at low Pd-loadings, like 0.02 mol% Pd, SMC could give yields up to 96% after 4 h. **Catalyst 1** could even promote catalysis at 0.0005 mol%, which is unusual among both heterogeneous and

homogeneous catalysts. Low catalyst loadings helps fulfil requirements of sustainable chemistry and reduces costs, waste generation, and health- and environmental risks.[24] Wang et al. did not measure TON for **catalyst 2**, thus evaluating which of catalysts 1 and 2 is most effective is difficult.
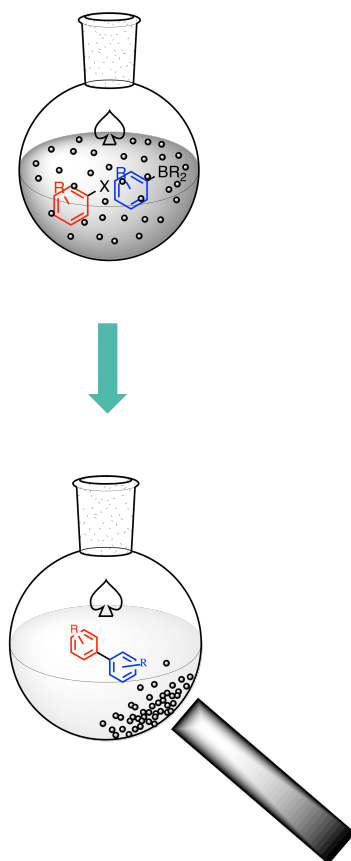


**Figure 3.3:** Synthesis of biaryls from SMC with MAGNPs, with external magnet separating MAGNPs from solution. Inspired by Sydnes[9]

Using a magnet to separate catalysts from solution allows for an easier, faster and a cleaner way of separation than conventional procedures like filtration and precipitation.[8] One may isolate the catalyst by withholding it in the reaction flask with an external magnet, as seen in Figure 3.3.[9] It was found that the magnetic response of the catalysts 1 and 2 were so sensitive that one minute was enough to separate the magnetic particles with a handheld magnet.[8] After each run, more than 99 weight percent (wt%) of the magnetic catalyst could be easily recovered with a handheld catalyst, indicating no significant decrease of efficiency during recycling. $Fe_3O_4$ is assumed to be bound covalently to nitrogen in catalysts 1 and 2, seen in Figure 2.4, thus the catalyst could be fully removed by using a magnet on $Fe_3O_4$.

Both of Wang et al.'s catalysts show promising results, where reagents may influence which catalyst is preferred. **Catalyst 1** is a sufficient catalyst for reactions with aryl bromides

at 70 °C and can perform for 21 runs, whilst **catalyst 2** can be preferred for aryl chlorides. **Catalyst 1** in Wang et al.'s research is one of the few catalysts that can be recycled that many times, making the results in their report extraordinary.[9] When comparing the performance for conversion of MAGNPs in Sydnes' 2017 report, there is significant differences in reusability.[9] As stated previously, Bourouina et al. reported on a Pd-NHC catalyst that could only be reused 6 times.[6] However, **Catalyst 1** and **2** shows the potential for MAGNP catalysts in industry. It seems like Wang et al.'s Pd-NHC MAGNPs are able to reduce Pd-leaching in a reaction with 4-bromoacetophenone and phenylboronic acid with promising yields.

# 4  Conclusion

Pd-leaching is one of the concerns regarding the Suzuki-Miyaura reaction (SMC). Pd-leaching can be significantly reduced in a reaction between 4-bromoacetophenone and phenylboronic acid with a stable heterogeneous Pd-NHC complex immobilized on magnetic carriers. Wang et al. developed two catalysts, **catalyst 1** and **2** in Figure 2.4, that demonstrated little leaching and redeposition for the reaction in Scheme 3 through trace analysis, hot-filtration tests and reusability tests. **Catalyst 1** experienced more leaching when reacting with aryl chlorides. **Catalyst 2** could activate aryl chlorides at higher temperatures without sufficient leaching due to having pyrridine as a ligand. Wang et al. proposed the electronic and steric stability of the different NHC-ligands to be the main reason for reduced Pd-leaching. **Catalyst 1** could also be recycled and used after 21 runs without significant decrease in yield. Both **Catalyst 1** and **2** could be removed by an external magnet. **Catalyst 1** may be preferred when reacting with aryl bromides at 70 °C due to higher yields (96-99%). **Catalyst 2** is more preferable when using aryl chlorides with a yield of 74% and little leaching. Magnetic catalysts makes cross-coupling reactions more sustainable by reducing Pd-leaching in the solvent and product and **Catalyst 1** is efficiently recycled.
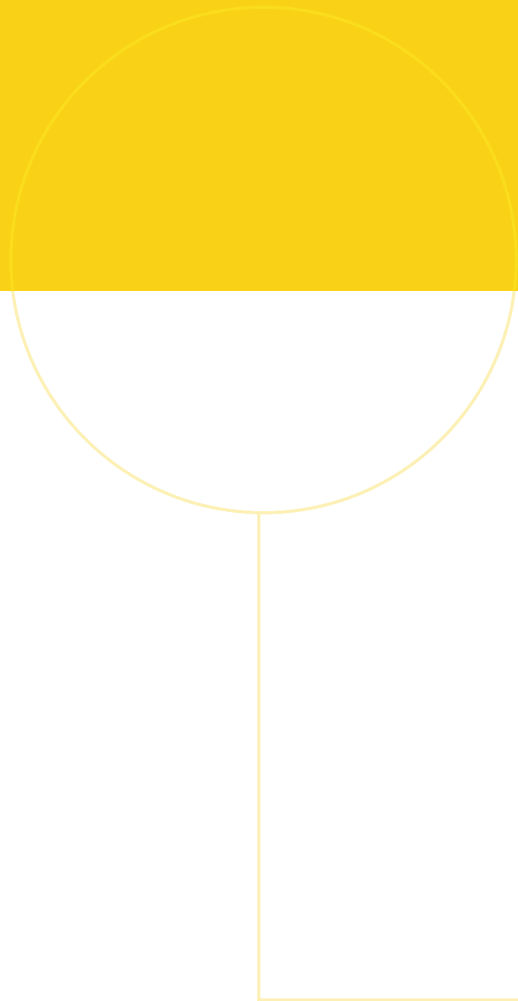
Trondheim, April 28, 2023

Katja L. Benestad

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